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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/026,362 | 12/21/2001 | Bernard D. Santarsiero | 22700-730 | 8186 |

7590 12/15/2004

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[REDACTED] EXAMINER

GAKH, YELENA G

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| | 1743 |

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

WV

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|------------------------------|------------------------|---------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/026,362 | SANTARSIERO ET AL. |
| | Examiner | Art Unit |
| | Yelena G. Gakh, Ph.D. | 1743 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 02 June 2003.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 57-84 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 57-84 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 21 December 2001 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>12/21/01, 12/12/02, 04/16/03, 04/22/03</u> <u>04/20/04</u> | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Preliminary amendment filed on 06/02/03 is acknowledged. Claims 57-84 are pending in the application.

Information Disclosure Statement

2. Due to overwhelming volume of IDS submitted for the instant application the examiner requests indicating relevance of the prior art to the subject matter of the present application and withdrawing irrelevant references from IDS in future submissions of IDS.

Specification

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to as not being written “in such full, clear, concise, and exact terms as to enable any person skilled in the art to” to practice the invention in its best mode.

Throughout the specification the term “mother liquor” is used in the context, which appears to contradict conventional meaning of this term. According to on-line Dictionary.com: “*mother liquor* is the impure or complex residual solution which remains after the salts readily or regularly crystallizing have been removed”; on-line MSDS HyperGlossary: “When a solid deposits from a solution the process is called crystallization if the solid is crystalline and precipitation if the solid is a powder or amorphous material. The solid that is formed is called the precipitate and the liquid solution that remains is called *the supernatant* or “*mother liquor*”. It is not clear from the specification, how operations involving “mother liquid” are related to the subject matter of the invention, i.e. the method and apparatus **for** crystallizing samples. As it is mentioned, the “mother liquor” is the solution remained after crystallization when the crystals

are removed, and therefore it is not apparent, how it can be used in the crystallization experiments. If the Applicants are using this term in a non-conventional manner, its definition should be clearly indicated in the specification.

4. The specification contains a plurality of typos, particularly related to the volume of the samples: it seems that in all cases the Greek letter μ is absent from μL , thus leaving L as a volume measure (starting with page 4). Appropriate corrections are required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 73-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 73, 77 and 81 recite a mother liquor drop station capable of simultaneous removing mother liquor from a plurality of wells and delivering it to drop regions (“at the same time”). The specification does not disclose an apparatus capable of simultaneous removing solutions from the microtiter plate and delivering them to a different area, since these operations can only be sequential. Thus, claims 73-84 are not enabled by the specification.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 57-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 57-84 recite manipulation with “mother liquor”, which has unclear meaning in the context of the present application. This renders the claims unclear and indefinite, since it is not

apparent from the specification, what this liquor is, and how the apparatus is supposed to operate in order to properly manipulate with it. For example, if the “mother liquor” is the solution formed after crystallization, does it mean that “a mother liquor station capable of removing mother liquor from a plurality of wells” should be capable of separating mother liquor, or supernatant, from the crystals?

From the claims it is not clear, what is the difference between two “drop stations”: “a mother liquor drop station” and “a molecule drop station”, which both should be capable of delivering samples to the same place. Moreover, since claims 70, 72, 73, and 81 recite in their bodies only stations capable of withdrawing solutions of volumes less than 25 nL from the wells of microtiter plate and delivering them to a different location, the examiner considers all fluid handling apparatus capable of these operations meeting the requirements of the pending claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

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evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. **Claims 57-60, 66-70 and 72** are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Hayes et al. (US 5,658,802), Ershow et al. (US 5,756,050), Brown et al. (US 5,807,522), Tisone et al. (US 6,063,339), Papen et al. (US 6,079,283), Little et al. (US 2001/0008615A1) or Bienert et al. (US 2001/0019845A1).

All indicated references disclose fluid handling systems capable of delivering plurality of samples withdrawn from multiwell plates in volumes less than 25 nL (20 nL, 15 nL), the system comprising a platform on which a multiwell plate is positionable. The systems are capable of delivering nanoliter drops into microtiter plate wells, on substrates, etc., which would include sitting drop regions. Piezoelectric valve or solenoid valve is conventionally used in these systems.

Although the references do not specifically indicate two fluid handling systems with similar capabilities, it would have been obvious for anyone of ordinary skill in the art to use two such systems, because this expands the area of application of such devices, including delivering nanoliter volumes of reagents from different reagent sources.

13. **Claims 61-65 and 71** are rejected under 35 U.S.C. 103(a) as being unpatentable over any of the prior art applied to claims 57-60, 66-70 and 72 above, in view of Meltzer (US 5,873,394, IDS).

While none of the prior art recited above discloses a cover slip station, Meltzer discloses “automated sample preparation workstation fro the vapor diffusion method of crystallization and method of preparation” (Title), with the apparatus comprising a cover slip station and fluid devices capable of delivering 1-10 μ L volumes of the compound to be crystallized (“a molecule drop”) and the mixing compound (“mother liquor”) to the plurality of cover slips.

It would have been obvious for any person of ordinary skill in the art to apply fluid handling systems of the prior art recited above in Meltzer’s automated sample preparation and crystallization because this application is one of numerous applications requiring handling of fluids in extremely small volumes, as indicated by Meltzer.

14. **Claims 57-65 and 70-72** are rejected under 35 U.S.C. 103(a) as being unpatentable over Meltzer in view of any of the prior art cited in subparagraph 12.

Melzer discloses “an automated sample preparation workstation and sample preparation method for the vapor diffusion method of crystallization which performs multiple processing functions such as pipetting, diluting, coverslip manipulations, plate greasing and the like under microprocessor control. The apparatus is responsive to operator-entered processing requests and performs complex and accurate processing functions. The disclosed apparatus is menu-driven and thus easy to learn and simple to operate” (Title). In particular, Melzer discloses “9. The small pipetting probe aspirates a small amount (1 to 10 ul's) of the compound to be crystallized from a vial and dispenses it onto the coverslip. 10. The small pipetting probe aspirates a small amount (1 to 10 ul's) from the well containing the mixing compound and places it onto the coverslip with the compound to be crystallized and mixes it” (col. 4, lines 38-44). While Melzer does no disclose fluid handling of smaller amounts of the samples, less than 25 nL, the prior art cited in subparagraph 12 discloses just that.

It would have been obvious for any of ordinary skill in the art to use fluid handling devices capable of manipulating with liquids of volumes less than 25 nL, as disclosed in the prior art of subparagraph 10 in Melzer’s crystallization workstation, because this allows delivery of more precise and accurate volumes, decreases time for crystallization, and increases the number of experimental sites due to a smaller volume of each site.

15. **Claims 66-69** are rejected under 35 U.S.C. 103(a) as being unpatentable over McPherson et al. (US 5,096,676, IDS) in view of any of the prior art cited in subparagraph 12.

McPherson discloses “an apparatus for growing diffraction quality, protein crystals by vapor diffusion techniques”, involving “sitting drop” method (Abstract). “The apparatus of the present invention overcomes many of the drawbacks of the prior art methods and devices by providing novel crystal growing apparatus which is inexpensive, easy to use and readily compatible with automatic pipetting, sample preparation and diffraction analysis equipment. Because of the unique design of the apparatus, laboratory technicians with no particular skills, or specialized training, can use the apparatus to grow high quality crystals in very large numbers for numerous uses, including the diffraction analysis of macromolecular structures”.

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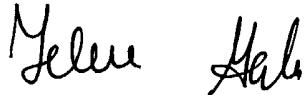
McPherson does not specifically disclose fluid handling apparatus capable of operating very small volumes of solutions (less than 15 nL). The prior art cited in subparagraph 12 discloses exactly such systems. It would have been obvious for any person of ordinary skill in the art to use modern sophisticated apparatus of the prior art recited in subparagraph 12 with McPherson's crystal growing apparatus, because McPherson specifically indicates that his apparatus is "easy to use and readily compatible with automatic pipetting, sample preparation and diffraction analysis equipment", and because the fluid delivery apparatus of the cited prior art are capable of delivering extremely precise volumes of solutions into the sitting drop microwells of McPherson's apparatus, which is very important for obtaining uniform crystals for X-ray analysis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh
12/10/04

A handwritten signature in black ink, appearing to read "Yelena Gakh".